REMARKS

Amendments to the Specification

The specification has been amended to update the priority information for the present application. The specification has also been amended to clarify the total number of parts for each figure in the Brief Description of the Drawings. No new matter has been added.

Amendments to the Claims

Claims 1-24 were pending. Claims 2-5 and 13-24 have been canceled. Claim 1 has been amended.

In particular, claim 1 has been amended to specify that the complex comprises monomeric IgA, or a portion thereof that binds to FcαRI, linked to a second portion which specifically binds the target cell or antigen. Support for the amendment of claim 1 can be found throughout the specification as filed, *e.g.*, original claim 3. No new matter has been added.

The foregoing amendments should in no way be construed as an acquiescence to any of the Examiner's rejections and was done solely to expedite prosecution. Applicant reserves the right to pursue the claims as originally filed in this or a separate application(s). No new matter has been added.

Rejection of Claims 1-12 Under 35 U.S.C. §102(b)

Claims 1-12 are rejected under 35 U.S.C. §102(b) "as being anticipated by Shen et al. (WO 98/23646) as evidenced by Monteiro *et al.* (J. Exp. Med. 171:597-613 (1990)) and the specification." Specifically, the Examiner states that:

> Shen *et al.* teach bifunctional antibodies comprising an antibody that binds FcαRI and a bacteria (see page 22) or cancer cell or antigen (see page 19-20) thereof wherein the binding is not inhibited by endogenous IgA (see page 4, lines 28-29), further is a method for eliminating cells or antigen in a subject by administration of the bispecific antibody to a subject (see page 28-29 . . . As evidenced by Monteiro *et al.* (and the specification at page 1, lines 6-8) there is only a single class of IgA Fc receptor, FcαRI, therefore since the antibody binds to FcαRI, it would be inherent that the antibody would bind to FcαRI expressed on Kupffer cells . . .

Applicant respectfully traverses this rejection.

The pending claims are drawn to methods for eliminating a target cell or antigen from the circulatory system of a subject comprising the use of a binding complex. Specifically, the binding complex comprises monomeric IgA, or a portion thereof that binds FcαRI, linked to a second portion which specifically binds the target cell or antigen.

Shen *et al.* fail to teach or suggest the claimed invention which is based on the discovery of a novel role for the immunoglobulin A (IgA) receptor, FcαRI (CD89), in immunity and, thus, a novel method for fighting infection. Specifically, as shown for the first time by the present invention, monomeric IgA plays an important role in systemic immunity by virtue of its interaction with FcαR expressed on liver Kupffer cells and other FcαR-expressing cells (*e.g.*, neutrophils) present at the interface of the mucosal and systemic immune systems (*e.g.*, the sinusoidal lining of the liver). FcαR expressed on these cells selectively binds and causes elimination (*e.g.*, phagocytosis) of monomeric IgA-antigen complexes by the cells. Accordingly, only monomeric IgA, and not dimeric (secretory) IgA, is capable of initiating phagocytosis by FcαRI-expressing Kupffer cells.

As described in Applicant's specification, in a transgenic mouse model, inflammatory mediators induce FcαRI expression on Kupffer cells, causing efficient phagocytosis of monomeric IgA-coated bacteria *in vivo*. Dimeric IgA does not initiate phagocytosis. Therefore, the present invention showed for the first time that monomeric IgA-FcαRI interactions on Kupffer cells provide a "second line" of defense in mucosal immunity, by eliminating invasive bacteria entering via the portal circulation and thus preventing disease.

Shen *et al.* do not recognize the distinct roles monomeric IgA and dimeric IgA play in immunostimulation, nor do Shen *et al.* teach or suggest a method of fighting infection using a complex containing monomeric IgA. Therefore, claims 1-12 are novel in view of Shen *et al.*

Rejection of Claims 1-7, 11, and 12 Under 35 U.S.C. §102(e)

Claims 1-7, 11, and 12 are rejected under 35 U.S.C. §102(e) "as being anticipated by van de Winkel (U.S. Patent No. 6,111,166, filed 6/27/97) and as evidenced by Monteiro *et al.*" Specifically, the Examiner states that:

> van de Winkel teach bifunctional antibodies comprising an antibody that binds FcαRI and a virus, bacteria, or fungus (see column 9, lines 58-60) or cancer cell or antigen

> (see column 9, lines 1-7) thereof wherein the binding is not inhibited by endogenous IgA (see column 7, lines 40-48), further is a method for eliminating cells or antigen in a subject by administration of the bispecific antibody to a subject (see Example V) . . . As evidenced by Monteiro *et al.* and the specification on page 1, lines 6-8 there is only a single class of IgA Fc receptor, FcαRI, therefore, since the antibody binds to FcαRI, it would be inherent that the antibody would bind to FcαRI expressed on Kupffer cells.

Applicant respectfully traverses this rejection.

As described above, the content of which is reiterated here, the presently claimed invention is based on the discovery that monomeric IgA plays an important role in systemic immunity by virtue of its interaction with FcαR expressed on liver Kupffer cells and other FcαR-expressing cells (*e.g.*, neutrophils) present at the interface of the mucosal and systemic immune systems (*e.g.*, the sinusoidal lining of the liver). The present invention showed for the first time that monomeric IgA-FcαRI interactions on Kupffer cells provide a "second line" of defense in mucosal immunity, by eliminating invasive bacteria entering via the portal circulation and thus preventing disease.

U.S. Patent No. 6,111,166 fails to recognize the distinct role that monomeric IgA plays in immunostimulation or to teach the presently claimed method of fighting infection using a complex composed, in part, of monomeric IgA. Therefore, claims 1-12 are novel in view of the cited references.

Rejection of Claims 1-12 Under 35 U.S.C. §103(a)

Claims 1-2 are rejected under 35 U.S.C. §103(a) "as being unpatentable over U.S. Patent No. 6,111,166 as evidenced by Monteiro *et al.* and the specification, as applied to claims 1-7, 11, and 12 above, and further in view of Morton *et al.* (Critical Reviews in Immunology 16:423 (1996))." In particular, the Examiner states that:

> van de Winkel has been described supra. van de Winkel also teach that FcαRI has an affinity that is increased upon exposure to GM-CSF (see column 5, lines 54-37). van de Winkel does not teach administration of GM-CSF to a subject which increases the expression of FcαRI of Kupffer cells. This deficiency is made up for by the teachings of Morton *et al.* [which] teach expression of FcαRI can be upregulated by many factors and cytokines, specifically TNF-α (see page 429).

Based on this, the Examiner concludes that:

> one of ordinary skill in the art would have been motivated to and had a reasonable expectation of success to have added a cytokine to the method of van de Winkel in view of the teachings of Morton *et al.* because van de Winkel teach the affinity of the FcαRI is increased upon adding cytokines . . . and because Morton *et al.* teach that the expression of the FcαRI is upregulated in many cell lines that express FcαRI . . .

Applicant respectfully traverses this rejection.

As described above with respect to the rejection of claims 1-7, 11, and 12 under 35 U.S.C. §102(e) in view of U.S. Patent No. 6,111,166, U.S. Patent No. 6,111,166 fails to teach or suggest the claimed invention. Morton *et al.* fails to cure the deficiencies of U.S. Patent No. 6,111,166. Like U.S. Patent No. 6,111,166, Morton *et al.* fail to recognize the distinct role that monomeric IgA plays in immunostimulation. Morton *et al.* also fail to teach or suggest a method of infection using a complex composed of monomeric IgA. Accordingly, claims 1-12 are patentable in view of the cited references.

CONCLUSION

Based on the foregoing, the claims are in condition for allowance. If a telephone conversation with Applicant's attorney would help expedite the prosecution of the above-identified application, the Examiner is urged to call Applicant's attorney at (617) 227-7400.

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Respectfully submitted,

By _____

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